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Title: (-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine hydrogensuccinate and malonate and the use thereof for the treatment of schizophrenia and psychoses

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Patent- og Varemærkestyrelsen
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13 September 2004

Susanne Morsing

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PATENT- OG VAREMÆRKESTYRELSEN

(-)-Trans-4-(6-chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine hydrogensuccinate and malonate and the use thereof for the treatment of schizophrenia and psychoses

The present invention relates to (-)-Trans-4-(6-chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine hydrogensuccinate or malonate, pharmaceutical compositions containing these salts and the use thereof for the treatment of schizophrenia and other psychoses.

Background of the Invention

The present invention relates to the treatment of Schizophrenia and other diseases involving psychotic symptoms.

The group of diseases including psychotic symptoms as a prominent aspect of their presentation includes: Schizophrenia, Schizophreniform Disorder, Schizoaffective Disorder, Delusional Disorder, Brief Psychotic Disorder, Shared Psychotic Disorder as well other psychotic disorders and diseases that present with psychotic symptoms.

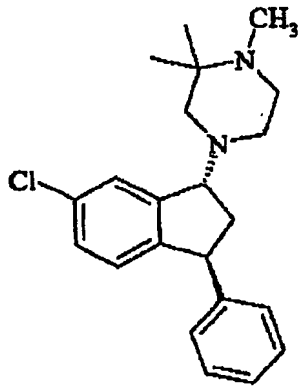
The aetiology of schizophrenia is not known, but the dopamine hypothesis of schizophrenia (Carlsson, Am. J. Psychiatry **1978**, 135, 164-173), formulated in the early 1960s, has provided a theoretical framework for understanding the biological mechanisms underlying this disorder. In its simplest form, the dopamine hypothesis states that schizophrenia is associated with a hyperdopaminergic state, a notion which is supported by the fact that all antipsychotic drugs on the market today exert some dopamine D_2 receptor antagonism (Seeman *Science and Medicine* **1995**, *2*, 28-37). The hyperdopaminergic hypothesis has recently been strongly supported by the direct evidence of increased stimulation of dopamine receptors by dopamine in schizophrenia (Abi-Dargham *et al. PNAS* **2000**, *97*, 8104-8109). However, whereas it is generally accepted that antagonism of dopamine D_2 receptors in the limbic regions of the brain plays a key role in the treatment of positive symptoms of schizophrenia, the blockade of D_2 receptors in striatal regions of the brain cause extrapyramidal symptoms (EPS).

However, studies have indicated that 5-HT_2 receptor antagonists may reduce extrapyramidal effects and improve the negative symptome of schizophrenia.

Central α_1 antagonistic actions may also contribute to improved antipsychotic properties because blockade of central α_1 receptors preferentially suppresses mesolimbic versus nigrostriatal dopaminergic transmission and furthermore facilitates thalamic gating of sensory input to the cortex, a process compromised in psychotic patients (Millan *et al*, *JPET*, **2000**, *292*, 38-53).

EP patent No. 638 073 covers a group of trans isomers of 3-aryl-1-(1-piperazinyl)indanes substituted in the 2- and/or 3-position of the piperazine ring. The compounds are described as having high affinity for dopamine D1 and D2 receptors and the 5-HT_2 the receptor.

The compound, which is the subject of the present invention has the general formula



(I)

and is covered generically by the claims of the above European patent. However, the specific enantiomeric form above has not been disclosed in the above European patent, which only describes trans isomers in the form of racemates.

The enantiomer of the formula (I) above has been described by Bøgesø et al. in J. Med. Chem., 1996, 38, page 4380-4392, in the form of the fumarate salt, see table 5, compound

(-)-38. This publication concludes that the (-)-enantiomers of compound 38 is a potent D_1/D_2 antagonists showing some D_1 selectivity in vitro while in vivo it is equipotent as D_1 and D_2 antagonist. The compound is described as a potent 5-HT_2 antagonist, having high affinity for α_1 adrenoceptors. Also it is mentioned that the compound does not induce catalepsy.

It has now, surprisingly, been found that the aqueous solubility of the succinate salt and the malonate salt of the compound of formula (I) is considerably larger than the aqueous solubility of the fumarate salt.

The succcinate salt was also found to be more stable than the fumarate salt and to be non-hygroscopic.

The physical properties of the salts of the invention indicate that they will be particularly useful as a pharmaceutical.

The Invention

Accordingly, the present invention relates to the succinate salt or the malonate of the compound of formula (I), a pharmaceutical composition containing these salts, the use of these salts for the preparation of a pharmaceutical composition and the use of these salts for the treatment of schizophrenia and psychoses.

The succinate salt according to the invention may be obtained by treatment of the free base of a compound of formula (I) with succinic acid in an inert solvent followed by precipitation, isolation and optionally recrystallization. If desired, the crystalline salt may thereafter be subjected to micronisation by wet or dry milling or another convenient process, or preparation of particles from a solvent-emulsification process.

Precipitation of the succinate salt of the invention is preferably carried out by dissolving the free base of the compound of formula (I) in a suitable solvent, such as acetone or toluene, and thereafter mixing this solution to a suspension of succinic acid in a suitable solvent, such as acetone or toluene. The suspension may be heated until all succinic acid has dissolved.

The succinate salt of the compound of the invention precipitated upon cooling of the solution. The succinate salt of the invention may optionally be recrystallised one or more times and isolated by filtration, washed and dried.

The malonate salt may be obtained using analogous procedures.

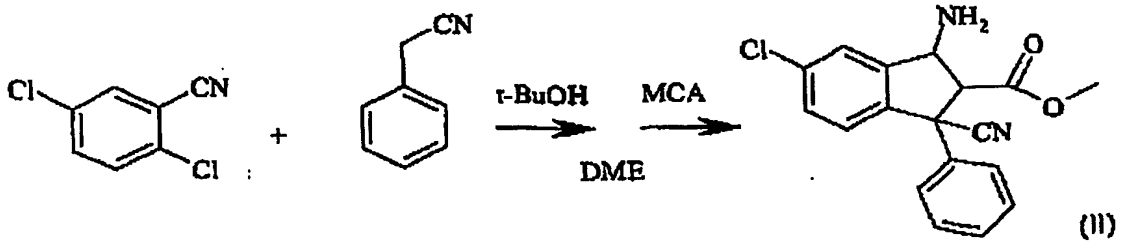
The invention also covers hydrates and solvates of the salts of the invention.

By hydrates is meant the salts of the invention containing chemically bound water molecules. One or more water molecules may be bound to each molecule of the compound of the invention. Hydrates are usually prepared by formation of the salt in presence of some water.

By solvates is meant the salts of the invention containing chemically bound solvent molecules. One or more solvent molecules may be bound to each molecule of the compound of the invention. Solvates are usually prepared by formation of the succinate salt in presence of the solvent.

The compound of formula (I) in racemic form may be prepared as described in EP patent No. EP 638 073 and in Bøgesø et al. J. Med. Chem., 1996, 38, page 4380-4392, it is described how optical resolution of the racemic compound may be accomplished by crystallisation of diastereomeric salts.

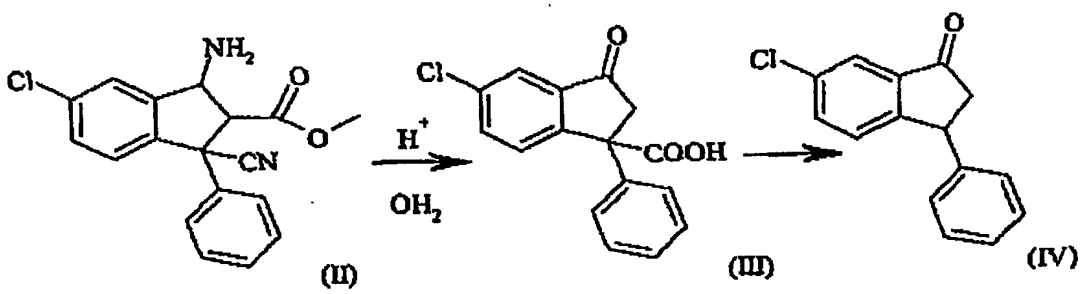
The enantiomer of formula (I) may also be obtained by a partly stereoselective process involving the following steps:



(II)

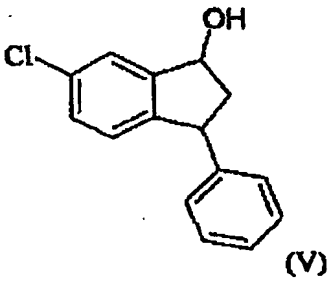
Benzyl cyanide is reacted with 2,5-dichlorobenzonitril in presence of a base, suitable potassium tert-butoxide, reaction with methyl chloro acetate (MCA) leads to spontaneous ringclosure and one pot formation of the compound of formula (II).

The compound of formula (II) is then subjected to acidic hydrolysis to form a compound of formula (III), suitable by heating in a mixture of acetic acid, sulphuric acid and water, and thereafter decarboxylation by heating the compound of formula (III) in a suitable solvent, such as N-methyl pyrrolidone, to form a compound of formula (IV).



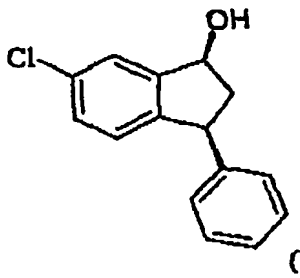
(II) (III) (IV)

The compound of formula (IV) is then reduced, suitably with $NaBH_4$ in ethanol, to form a compound of formula



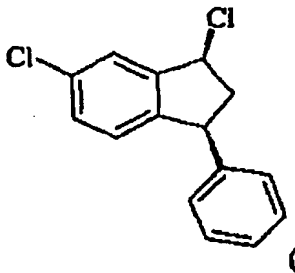
(V)

The compound of formula (V) is resolved on a chiral column, suitably using CHIRALPAK AD as the stationary phase, to achieve the desired enantiomer of formula



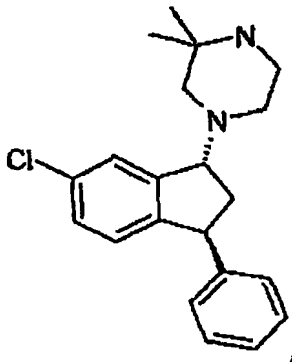
(Va)

The alcohol group of the cis-alcohol of formula (Va) is converted to a suitable leaving group, such as halogen or a sulphonate, suitable by reaction with an agents, such as thionylchloride, mesylchloride and tosylchloride, in an inert solvent, suitable tetrahydrofuran. The cis-chloride having the formula



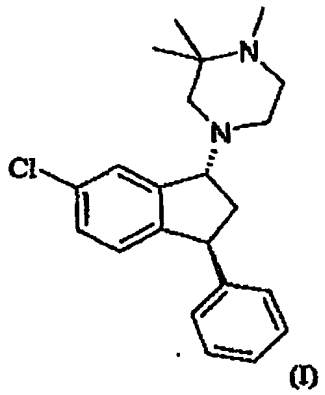
(VI)

is then reacted with 2,2-dimethylpiperazine in a suitable solvent, such as methyl ethyl ketone in presence of a base, such as potassium carbonate. The resulting compound of formula



(VII)

is methylated at the secondary amine functionality, suitable by reductive amination of an aldehyde, such as formaldehyde, paraformaldehyde and trioxane, to obtain the free base of a compound of formula



(I)

It has been found that impurities in the form of the corresponding cis-enantiomer may effectively be removed by precipitation of the fumarate salt of the compound of formula (I) optionally followed by one or more re-crystallisations.

Impurities in the form of the cis-enantiomer may also be removed, by precipitation of the fumarate salt of the compound of formula (VII) optionally followed by one more more re-crystallisations.

The salts of the invention may be administered in any suitable way e.g. orally, buccal, sublingual or parenterally, and the salts may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the salts of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule.

Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants, fillers and diluents and subsequently compressing the mixture in a convenient tabletting

machine. Examples of adjuvants, fillers and diluents comprise corn starch, lactose, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

Solutions for injections may be prepared by dissolving the salts of the invention and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to desired volume, sterilisation of the solution and filling in suitable ampules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

The daily dose of the compound of formula (I) above, calculated as the free base, is suitable between 1.0 and 160 mg/day, more suitable between 1 and 100 mg, and more preferred between 3 and 55 mg.

The invention will be illustrated in the following examples.

Example 1

(-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine free base

(-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine, hydrogenfumarate (25,0 grams) is suspended in toluene (125 ml). Aqueous ammonia 25% (75 ml) is added. The three phase is stirred until all solids have disappeared. The organic phase is separated, and the aqueous phase is washed with toluene (25 ml). The combined extract and toluene wash is washed with water (25 ml). The aqueous phase is discarded and the organic phase is dried by sodium sulphate sicc. (35 grams), the slurry is filtered and the filtrate is evaporated to dryness on a rotary evaporator. The crude free base (15 grams) is used without further purification.

Example 2

(-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine hydrogen succinate

Crude (-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine (8,50 grams) is dissolved in acetone (30 ml). A suspension of succinic acid (3,25 grams) in acetone (32 ml) is prepared and the (-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine solution is added, the succinic acid dissolves and shortly the (-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine hydrogen succinate precipitates. The suspension in cooled to 0°C for 90 minutes before to precipitate is isolated by centrifugation. The supernatant is discarded and the precipitate is washed with acetone (20 ml). The slurry is centrifuged and the supernatant is discarded and the precipitate is dried "in vacuo" at 50°C.

Example 3

(-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine free base

(-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-3,3-dimethylpiperazine (9,9 grams) is dissolved in formic acid (10,5 ml) and to the solution is added formaldehyde (10,5 ml). Heated to 60°C and kept at this temperature for 2½ hours. After cooling of reaction mixture water (50 ml) and hexane (50 ml) is added. Adjustment of pH with NaOH (27%, 33 ml) to pH > 12. Hexane phase washed with aq. NaCl (20 ml) and water (20 ml). Hexane exchanged azeotropic with acetone (90 ml) and concentrated. The crude free base in acetone (10 ml) is used without further purification.

Example 4

(-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine hydrogen succinate

Crude (-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine in acetone solution (10 ml). A suspension of succinic acid (3,4 grams) in acetone (20 ml) is prepared and the(-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine solution is added and the mixture is heated to reflux (55°C). The succinic acid dissolves and during cooling of the solution (-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine hydrogen succinate start precipitating. Suspension left overnight to precipitate. (-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine hydrogen succinate is isolated by filtration and washed with acetone (20 ml). Product is dried "in vacuo" at 60°C.
Yield: 7,9 grams, 64% based on 1-(6-Chloro-3-phenyl-indan-1-yl)- 3,3-dimethyl-piperazine.
Mp: 140-141 °C

Example 5

Solubility of the fumarate salt and other salts of the compound of formula (I)

The solubility of the salts in water was determined by adding 20 mg of salt to 2 ml of water. The suspensions were left at the rotarmix for at least 24 hours, and subsequently pH was measured and the concentration was determined by HPLC. The solid precipitate was isolated and left to dry in the laboratory. The results are summarized in table 1.
In the solubility determinations of the succinate, 20 mg were dissolved and more solid was added until solid precipitate was present.

Table 1: Solubility of the salts in water at room temperature.

Sample	Batch	pH	Solubility(mg/ml)
Succinate 1:1 (U)	282/066B	4,37	23,37
Malonate 1:1	282/067B	3,93	14,70
Fumerate (F)	174/125	3,77	1,48

Example 6

The stability of the salts was investigated under the following circumstances:

Heat, 60°C/80%RH: Samples were stored at 60°C with 80%RH for one week. Then they were dissolved and analysed by HPLC.

Heat, 90°C: Samples (~10 mg) were stored at 90°C in closed containers containing 1 droplet of water. Then they were dissolved and analysed by HPLC.

Light: Samples were placed in the light cabinet at 250 w/m^2 for 24 hours. Then they were dissolved and analysed by HPLC.

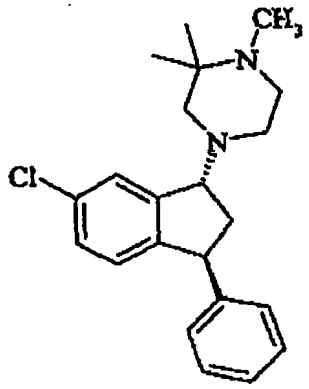
The area of peaks in the chromatograms besides the peaks corresponding to the substance or the acid was summarized. The succinate salt of the invention does not show any degradation at all.

Example 7

The hygroscopicity of the succinate salt was investigated by Dynamic Vapour sorption (DVS) and the salt was found to be non-hygroscopic.

Claims:

1. A succinate salt or malonate salt of the compound of formula



(I)

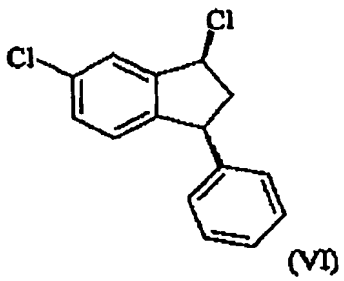
2. A succinate salt according to claim 1 which is the 1:1 salt of (-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine and succinic acid in the form of a crystalline anhydrate.

3. A pharmaceutical composition comprising a salt according to any of claims 1-2 together with at least one pharmaceutically acceptable carrier, filer or diluent.

4. The use of a salt according to any of claims 1-2 for the preparation of a pharmaceutical composition for the treatment of schizophrenia and other psychotic disorders.

5. A method for the treatment of schizophrenia and other psychotic disorders comprising administering a therapeutically effective amount of a salt according to any of claims 1-2 to a subject suffering from such a disorder.

7. A method for the preparation of a compound of formula (I) comprising reacting a compound of formula



(VI)

with 2,2-dimethylpiperazine in presence of a base, followed by reductive amination with aldehyde compounds, such as formaldehyde, paraformaldehyde or trioxane followed by isolation of the compound of formula (I) as the free base or a as a salt thereof.

8. The method according to claim 7 wherein the compound formed is the succinate salt of the compound of formula (I).

9. The method according to claim 7 wherein the base of formula (I) obtained is first isolated as the fumarate salt thereof, which is optionally recrystallised one or more times, the salt fumarate salt is then treated with a base to liberate the free base of the compound of formula (I) which is then converted to the succinate salt thereof.

Abstract

(-)-Trans-4-(6-Chloro-3-phenylindan-1-yl)-1,3,3-trimethylpiperazine hydrogensuccinate or malonate, pharmaceutical compositions containing these salts and the use thereof for the treatment of schizophrenia and other psychotic disorders.